General

Guideline Title

The role of liver resection in colorectal cancer metastases.

Bibliographic Source(s)

Gallinger S, Biagi JJ, Fletcher GG, Nhan C, Ruo L, McLeod RS, Expert Panel. The role of liver resection in colorectal cancer metastases. Toronto (ON): Cancer Care Ontario (CCO); 2012 Jun 15. 44 p. (Evidence-based series; no. 17-7). [86 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

1. What is the role of liver resection in patients with extrahepatic metastases (EHM)?
   1a) *Pulmonary Metastases*

   Patients with liver and lung metastases should be seen in consultation by a thoracic surgeon. Combined or staged metastasectomy is recommended when, taking into account anatomic and physiologic considerations, the assessment is that all pulmonary metastases can also be completely removed. Furthermore, liver resection may be indicated in patients who have had a previous lung resection, and vice versa.

   1b) *Portal Node Metastases*

   Routine liver resection is not recommended in patients with portal nodal disease. This group includes patients with radiologically suspicious portal nodes or malignant portal nodes found preoperatively or intraoperatively. Liver plus nodal resection, along with perioperative systemic therapy, may be an option, after a full discussion with patients, in cases with limited nodal involvement and metastases that can be completely resected. Chemotherapy is discussed in Question 2 below.

   1c) *Metastases at Other Sites*

   Routine liver resection is not recommended in patients with non-pulmonary EHM. Liver plus extrahepatic resection along with perioperative

systemic therapy may be an option, after full discussion with patients, for metastases that can be completely resected. Chemotherapy is discussed in Question 2 below.

2. What is the role of chemotherapy in the surgical management of colorectal cancer (CRC) liver metastases?
   2a) *Resectable disease: Does perioperative chemotherapy result in an improved outcome in patients having liver resection for CRC metastases?*

   Perioperative chemotherapy, either before and after resection, or after resection, is recommended in patients with resectable liver metastatic disease. This recommendation extends to patients with extrahepatic metastatic disease that can be completely resected (R0). Risks and potential benefits of perioperative chemotherapy should be discussed in patients with resectable liver metastases.

   2b) *Initially unresectable disease: Should liver resection be performed in patients with initially unresectable metastatic liver disease following conversion chemotherapy?*

   Liver resection is recommended in patients with initially unresectable metastatic liver disease who have sufficient downstaging response to conversion chemotherapy. If complete resection has been achieved, postoperative chemotherapy should be considered

3. What is the role of liver resection when one or more liver metastases have radiographic complete response (RCR) following chemotherapy?
   - Surgical resection of all lesions, including lesions with RCR, is recommended when technically feasible and adequate functional liver can be left as a remnant. When a lesion with RCR is present in a portion of the liver that cannot be resected, surgery may still be a reasonable therapeutic strategy if all other visible disease can be resected.
   - Postoperative chemotherapy might be considered in these patients. Close follow-up of the lesion with RCR is warranted to allow localized treatment or further resection for an in-situ recurrence.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Colorectal cancer (CRC) metastases (liver metastases plus pulmonary metastases, portal nodal disease, or other extrahepatic metastases [EHM])

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Colon and Rectal Surgery

Gastroenterology

Oncology

Radiology

Surgery

Thoracic Surgery

Intended Users

Physicians

Guideline Objective(s)

- To evaluate if surgery should be considered for colorectal cancer (CRC) patients who have liver metastases plus (a) pulmonary metastases, (b) portal nodal disease, or (c) other extrahepatic metastases (EHM)
- To evaluate the role of chemotherapy in the surgical management of CRC with liver metastases in (a) patients with resectable disease in the liver, or (b) patients with initially unresectable disease in the liver that is downsized with chemotherapy (conversion)
- To evaluate the role of liver resection when one or more CRC liver metastases have radiographic complete response (RCR) following chemotherapy

Target Population

Patients with liver metastases from colorectal cancer (CRC) who have had or will have a complete (R0) resection of the primary cancer and who are being considered for resection of the liver or liver plus extrahepatic metastasis (EHM) with curative intent

Interventions and Practices Considered

1. Liver resection
2. Perioperative chemotherapy, either before and after resection, or after resection

Major Outcomes Considered

- Three- and five-year survival rate
- Median survival time
- Progression-free survival
- Complete clinical response
- Recurrence rate
- Postoperative complications and chemotherapy-related hepatic injury

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic review addressing the above questions was prepared by members of the Surgical Oncology Program at Cancer Care Ontario (CCO) together with a team of Ontario surgeons and oncologists (see the "Availability of Companion Documents" field).

Literature Search Strategy

MEDLINE and EMBASE databases were searched in January 2010, using the terms 'colorectal neoplasm' or 'colorectal cancer' as text or MeSH/EMBASE subject headings. These results were combined with 'liver neoplasm,' 'hepatectomy,' 'hepatic surgery,' and 'liver resection.' In

addition, the reviewer consulted with content experts and hand-searched the reference lists of the included articles and review articles found in the search. The results were restricted to full English language reports of human studies published from 1995 to the first week of January 2010.

Study Selection Criteria

Inclusion Criteria

- Randomized controlled trials (RCTs) with >50 patients
- Prospective or retrospective case series with the following:
    a. Question 1c, 2a, 2b: >50 patients*
    b. Question 1a, 1b: >25 patients*
    c. Question 3: No sample size limit

*Total number of patients in the study; the number of patients with the disease of interest was often less.

Exclusion Criteria

- Editorials, letters, comments; narrative reviews, unless there was an explicitly defined systematic literature search
- Studies assessing radiofrequency ablation, portal vein embolization, hepatic arterial infusion for administering chemotherapy, photodynamic therapy, or repeat liver resections. Studies using (but not focusing on or assessing) these techniques in conjunction with liver resection were not excluded.
- Studies reporting treatment of primary colorectal cancer (CRC) only
- Studies assessing liver transplantation
- Studies reporting only markers and enzymes outcomes or quality of life outcomes

For portal nodal disease, one additional study was located from the reference lists.

Number of Source Documents

A total of 83 articles were retained for inclusion in the review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

A systematic review addressing the above questions was prepared by members of the Surgical Oncology Program at Cancer Care Ontario (CCO) together with a team of Ontario surgeons and oncologists (see the "Availability of Companion Documents" field).

One reviewer extracted the data, and in cases of uncertainty the results were reviewed by a second reviewer.

Compilation of Study Results

The data from the relevant publications were extracted and compiled in a separate table for each question.

See Appendix 1 in the original guideline document for the A Measurement Tool to Assess Systematic Reviews (AMSTAR) rating of systematic

review.

Additional Literature Review

During the reading of the systematic review and preparation of the guideline recommendations by the Working Group, the Group determined that additional information from the included studies might be important in their interpretation. For the question on portal nodes, the study location (surgical centres), time period, macroscopic or microscopic involvement, and chemotherapy given were recorded. Some of the other studies were reexamined where the results appeared unclear or inconsistent.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Program in Evidence-based Care (PEBC) is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle. The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by PEBS Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Cancer Care Ontario Surgical Oncology Program (CCO SOP) considered this topic to be of high priority because of advances in chemotherapy and expanding indications for liver resection. A working group of clinical experts was established to prepare a systematic review on the role of liver resection for colorectal cancer metastases. The PEBC was then contacted to continue the process by preparing a practice guideline based on this systematic review, including the regular internal and external review process, professional consultation, and knowledge dissemination. The final version of the systematic review incorporated feedback obtained during the guideline development process.

This EBS was developed by the Working Group and the Expert Panel which were constituted for the development of this guideline. The series is a convenient and up-to-date source of the best available evidence on the role of liver resection in colorectal cancer (CRC) metastases, developed through a review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario. The participants represented the various sites in Ontario designated as Hepatic, Pancreatic, and Biliary Tract (HPB) surgical centres meeting the Standards set by CCO. HPB surgeons and medical oncologists were part of the Working Group, while the Expert Panel also included radiologists, general surgeons, and a thoracic surgeon.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP)

Prior to the submission of this Evidence-Based Series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The report was approved by the RAP with the suggestions for minor changes and the Working Group responses.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, Sections 1 and 2 were circulated to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, five targeted peer reviewers from Ontario and Alberta considered to be clinical and/or methodological experts on the topic were identified by the Hepatic, Pancreatic, and Biliary tract (HPB) Surgical Oncology working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 9, 2012. Follow-up reminders were sent at two weeks and at four weeks. The HPB Surgical Oncology working group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals in Ontario who are the intended users of the guideline. The survey was distributed by email to HPB Community of Practice members (excluding those on the Expert Panel), surgical oncology leads for each area of Ontario, Thoracic Community of Practice members, medical oncologists with gastrointestinal (GI) interest/expertise, and general surgeons with GI interest.

Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document), and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on February 9, 2012. The consultation period ended on March 18, 2012. The HBP Surgical Oncology Working Group reviewed the results of the survey.

See section 3 of the original guideline document for more information.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Most of the studies included are retrospective or prospective case series. In addition, there are three reports of randomized control trials (RCTs) of chemotherapy.

As indicated in the Key Evidence and Qualifying Statements following each recommendation in the original guideline document, many of the studies available for this review are non-comparative studies, with a lower quality of evidence than from RCTs.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Better understanding of the role of liver resection in colorectal cancer (CRC) metastases
- Refer to the "Key Evidence" sections of the original guideline document for details of evidence supporting each recommendation, including survival benefits of liver resection and chemotherapy in specific patient groups.

Potential Harms

- In the European Organization for Research and Treatment of Cancer (EORTC) Intergroup trial 40983, reversible postoperative complications occurred more often after chemotherapy than with surgery alone (25% versus 16%; p=0.04).
- Prolonged chemotherapy can result in liver toxicity, surgical complications, and increased morbidity.

Qualifying Statements

Qualifying Statements

- *Pulmonary metastases*. While the literature review tabulates the numbers of cases by the order of resection (in some studies, the data are actually for the occurrence of metastases), most of the original publications do not subdivide survival data according to the timing of resection. The order of surgery is often a reflection of the order of occurrence and not a surgical choice. In cases of simultaneous hepatic and pulmonary metastases, several of the included studies state that hepatic metastasectomy was performed first. One study indicates that this was to maintain pulmonary reserve and rule out unexpected extrahepatic abdominal disease; lung resection was performed six weeks later. Patients with either completely resected lung or liver metastases who later developed metastases at the other site were not explicitly addressed in the review article; however, the evidence suggests that prior metastasectomy should not exclude the resection of new metastases.
- *Portal node metastases*. Evidence is limited and based on prospective and retrospective case series of heterogeneous design. Studies include small numbers of highly selected patients, with surgery performed in a limited number of highly specialized centres. The location of nodes, microscopic or macroscopic involvement, type of surgery, extent of lymphadenectomy (complete/regional/selected nodes), use and type of chemotherapy, and presence of other extrahepatic metastases (EHM) are not consistent across the studies. Five-year follow-up is incomplete in several publications. Some studies conclude that portal nodal involvement should not be considered an absolute contraindication for the resection of colorectal liver metastases. The improvement in surgical techniques, preoperative treatment, and use of more effective chemotherapeutic agents all likely contributed to better survival in some of the recent studies. Some members of the Expert Panel suggested resection only in patients with metastases that respond to chemotherapy. While one group of researchers used this criterion in their study, presumably based on their previous results, other publications concluded the response to neoadjuvant chemotherapy did not correlate with overall survival. No consensus was reached on this issue.
- *Metastases at other sites*. There appears to be an increasing number of institutions performing combined liver resection and resection of EHM, although the evidence on outcomes is heterogeneous. The definitions for the site of disease, presentation of disease, and type of surgery performed differ among studies. Only four studies reported separate data for multiple extrahepatic sites other than the hepatic lymph nodes.
- *Resectable disease*. While results from confirmatory trials are awaited, the results from current evidence demonstrate consistent trends that favour perioperative chemotherapy, to the extent that there has been a widespread change in practice provincially and across other jurisdictions for the routine use of perioperative chemotherapy. See the original guideline document for additional qualifying statements related to resectable disease.
- *Initially unresectable disease*. While multiple studies have suggested that some patients can be made resectable via chemotherapy, there are no randomized controlled trials (RCTs), and these studies are largely case series. Different definitions of resectable were used. There is no expectation that an RCT with a non-surgical arm will be initiated in this patient population. Nonetheless, the data point to the potential for long term survival that has resulted in strong consensus in the oncology community for the widespread adoption of conversion chemotherapy with surgical intent. See the original guideline document for additional qualifying statements related to recommendations on initially unresectable disease.
- Some studies provide evidence that a large proportion of liver metastases with radiographic complete response (RCR) still contain viable tumour cells, but the studies were not designed to compare long-term survival between patients with RCR lesions that were resected and those that were left in place. The extrapolation of data from other studies suggests that resection should improve survival. Several articles on downstaging recommend limiting the duration of presurgical chemotherapy in order to minimize areas of liver metastases with RCR, which are then difficult to locate and resect. These studies used repeat imaging during chemotherapy with resection as soon as was technically feasible.

- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Gallinger S, Biagi JJ, Fletcher GG, Nhan C, Ruo L, McLeod RS, Expert Panel. The role of liver resection in colorectal cancer metastases. Toronto (ON): Cancer Care Ontario (CCO); 2012 Jun 15. 44 p. (Evidence-based series; no. 17-7). [86 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Jun 15

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Expert Panel and Working Group on the Role of Liver Resection in Colorectal Metastases

Composition of Group That Authored the Guideline

Working Group Members: Dr. Steven Gallinger* (*Chair*), Surgeon, University Health Network, Toronto, Ontario; Dr. James J. Biagi*, Medical Oncologist, Cancer Centre of South-eastern Ontario, Queen's University, Kingston, Ontario; Glenn G. Fletcher*, Research Coordinator, PEBC, Cancer Care Ontario/McMaster University, Hamilton, Ontario; Amber Hunter, Manager, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario; Cindy Nhan*, Project Coordinator, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario; Dr. Leyo Ruo*, Surgeon, McMaster University Medical Centre, Hamilton, Ontario; Dr. Robin S. McLeod*, Surgeon, Mount Sinai Hospital and Lead, Quality Improvement & Knowledge Transfer, Surgical Oncology Program, Cancer Care Ontario, Toronto, Ontario

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*Author of the review article on which this guideline is based.

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors and external reviewers were asked to disclose potential conflicts of interest. One of the authors (SG) received Hepatic, Pancreatic, and Biliary Tract (HPB) Fellowship Support from Sanofi and from Roche. The other authors reported that they had no conflicts of interest. One external reviewer indicated that he had written an editorial/opinion piece and helped organize a consensus conference on this topic. The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, et al. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. Surgery 2012;151(6):860-70. Electronic copies: Available to subscribers from the Surgery Journal Web site.
- The role of liver resection in colorectal cancer metastases. Summary. Toronto (ON): Cancer Care Ontario; 2012 Jun 15. 16 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.
- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available in Portable Document Format (PDF) from the CCO Web site.

Patient Resources

None available

NGC Status

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